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Is Intravenous Peramivir 300mg Effective and Safe In Treating Seasonal Influenza?

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A SELECTIVE EVIDENCE BASED REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

A. **Objective:** The objective of this selective EBM review is to determine whether or not intravenous Peramivir 300mg is effective and safe in treating seasonal influenza.

B. **Study Design:** Review of two randomized controlled trials (RCTs) and one randomized open-label study, all published in 2010, 2011, and 2014, respectively.

C. **Data sources:** Two randomized controlled trials and one randomized open-label study were all researched through the use of PubMed and belonged to peer reviewed journals.

D. **Outcome(s) Measured:** Primary efficacy endpoint analyzed was time to alleviation of symptoms measured by influenza symptom severity scale (ISS), a self-assessment four point scale. The primary safety endpoint measure was incidence of adverse events. The Fischer's exact test was used for intergroup comparison of the safety endpoint.

E. **Results:** When comparing alleviation of symptoms in all three studies, 300mg Peramivir was as effective as 600mg Peramivir. Both Peramivir groups were superior to the efficacy of placebo. Analysis of safety, using adverse events, displayed no significant difference between 300mg Peramivir and comparison groups.

F. **Conclusions:** After analysis of the three studies in this review, there is significant data to show 300mg Peramivir is effective and safe in treatment of seasonal influenza.

G. **Key Words:** Influenza, Peramivir

1. Introduction

Seasonal influenza is a viral respiratory infection that is highly contagious and in serious cases can lead to death. This paper evaluates two randomized controlled trials (RCTs) and one randomized open-label study comparing the efficacy and safety of intravenous Peramivir 300mg for the treatment of seasonal influenza.

Seasonal influenza is easily transmittable and currently affects over 10% of the population in the United States. It leads to 200,000 hospitalizations and approximately over 25,000 deaths, per year, in the United States.¹ Patients with an underlying chronic respiratory disease or who are elderly have a significantly increased chance of death if infected by the seasonal influenza virus, thus making prophylaxis an essential aspect in combating this virus.¹

The CDC has conducted data research and found that approximately \$10.4 billion is spent on direct medical expenses for influenza.² The CDC estimates, that there exists almost an 87 billion dollar economic burden from influenza in the United States. According to the CDC, there are approximately 31.4 million outpatient visits for flu each year.²

The presentation and complications of influenza are known. Much research has been conducted to understand the different strains of influenza that affect the human population. It is unknown which strains will be affecting the population and when the flu season will occur for a given year. There are vaccines available yearly to attempt and determine the most likely strains that the population will be exposed to.

Supportive care is the main treatment for uncomplicated patients which includes analgesics and rest. Antivirals are chosen for complicated or higher risk patients such as neuraminidase inhibitors (Oseltamivir and Zanamivir) and M2 inhibitors (Amantadine and Rimantidine).³

Most influenza cases are self-limiting thus the medications mentioned help combat the virus in those at high risk or complicated cases.³ The medications are effective for improvement of symptoms but do not cure the patient. Neuraminidase inhibitors are able to combat surface antigens of the virus.³ An issue affecting the treatment of influenza before the consideration of Peramivir, is the lack of options for route of administration.¹ The neuraminidase inhibitors approved in the United States before Peramivir are Oseltamivir and Zanamivir.³ Oseltamivir and Zanamivir are only available as oral or inhalation, respectively.³ Peramivir can have the potential to be an effective choice from the neuraminidase inhibitors due to its unique characteristic of being intravenously administered.¹ If Peramivir can prove to be effective and safe in treating influenza, it can provide a unique option for management.

2. Objective

The objective of this selective EBM review is to determine whether or not intravenous Peramivir 300mg is effective and safe in treating seasonal influenza.

3. Methods

For this review, specific criteria were met based on two randomized controlled trials (RCTs) and one randomized open-label study. The target population utilized was patients ≥ 14 years of age with influenza. The intervention analyzed was IV Peramivir 300mg which was further compared to IV Peramivir 600mg and Oseltamivir 75mg. The outcomes measured were time to alleviation of symptoms and incidence of adverse events.

In the Ison et al¹, an open label randomized study, the population consisted of 234 hospitalized patients aged 14 to 92 with seasonal influenza from 59 hospitals in the US, Canada, Mexico, Australia, and New Zealand. The subjects screened were randomized evenly into two groups of 117 subjects, one group receiving 300mg Peramivir twice daily and the other 600mg

Peramivir once daily, respectively. The duration of treatment was for 5 days unless the PCR showed detectable virus on day 4 of the course. In this case, the treatment was allowed to continue for 5 more days, for a total of 10 days.¹

The study by Kohno et al⁴, a double blind randomized controlled trial, included 300 previously healthy adults from 75 hospital centers in Japan. All subjects were aged 20-64 and recruited within 48 hours of influenza symptom onset. Influenza was confirmed in every subject by a positive rapid antigen test. The 300 subjects were randomized into three groups: 99 subjects receiving one single dose of 300mg intravenous Peramivir, 97 subjects receiving single dose of 600mg intravenous Peramivir, and 100 subjects receiving an equivalent single dose of placebo.⁴

The Kohno et al⁵ study, a multicenter double blind randomized control trial, incorporated 1,091 patients aged 20 years or older infected with influenza A or B virus. Subjects were from 146 institutions located in Japan, South Korea, and Taiwan. The subjects were divided into three groups receiving a single dose of intravenous 300mg Peramivir, a single dose of intravenous 600mg Peramivir, and 75mg of oral Oseltamivir twice daily for 5 days, respectively.⁵

I personally, conducted all of the research for this review via Pubmed NCBI and had selected the articles by relevance to my clinical question and meeting the criteria of including patient oriented outcomes (POEMS). The key words used in the searches were “Influenza” and “Peramivir”. All of the articles were published in English and met the criteria of being published in peer reviewed journals. All of the studies included in this review were published within the past 15 years and at least 2 of the studies were RCTs. Studies that included patients less than 14 years of age infected by seasonal influenza were excluded in the review. The statistics reported or used in the articles were p- values, relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH).

Table 1 - Demographics & Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Ison ¹ (2014)	Open Label RT	234	≥14	Patients from 59 hospitals ≥14 years of age with local influenza activity in the US, Canada, Mexico, Australia, and New Zealand	Patients who required dialysis, altered neurological status, undergoing systemic chemotherapy or radiotherapy, recent hematopoietic stem cell or organ transplant, uncontrolled HIV, pre-existing chronic infection, had CF, pre-specified abnormalities on lab testing, women who were pregnant	54	IV Peramivir 300mg bid for 5 days VS. IV Peramivir 600mg qd for 5 days
Kohno ⁴ (2010)	Double blind RCT	300	20-64	Patients who were healthy adults aged 20-64 with a positive influenza virus rapid antigen test recruited w/i 48hrs of onset	Patients with respiratory dysfunction requiring medication, neurologic symptoms, active chronic illness or HIV, on hemodialysis, bacterial infection, hx with steroids use of anti-influenza virus drugs w/in past 7 days, hx of hypersensitivity or serious ADRs to anti-influenza drugs, pregnant/breastfeeding	4	IV Peramivir 300mg qd for 1 day VS. IV Peramivir 600 mg qd for 1 day
Kohno ⁵ (2011)	Double blind RCT	1091	≥20	Patients aged 20 years or older with influenza A or B virus infection in 146 medical institutions in Japan, South Korea, and Taiwan	Patients with impaired respiratory function, history of CHF, poorly controlled DM, immunosuppressive therapy or AIDS, renal disorder, ischemic heart disease or serious arrhythmia, corrected QT interval or bradycardia, required hospitalization, infection requiring systemic antibiotics	8	IV Peramivir 300mg qd for 1 day VS. IV Peramivir 600mg qd for 1 day VS. Oseltamivir 75mg bid for 5 days

4. Outcomes

The outcomes addressed in this review consisted of patient oriented evidence found in the studies. In the Ison et al¹ study, time to alleviation of symptoms was measured (in hours) using a four point scale that was filled out twice daily from day 1 to 9 then once daily until day 14. The scale was utilized by patients to rate their influenza symptoms, specifically cough, sore throat, nasal congestion, myalgia, headache, feverishness, and fatigue. The study measured adverse events by a daily checklist represented by a percentage.¹

In Kohno et al⁴ and Kohno et al⁵, the primary efficacy endpoint analyzed was time to alleviation of symptoms. This was similarly recorded using a four point scale self-assessment, influenza symptom severity scale (ISS), rating the seven influenza symptoms mentioned above, twice daily for day 1 to 9 then once daily until day 14. The scale represented 0 meaning absent; 1, mild; 2, moderate; 3, severe. Alleviation was considered the time (in hours) when all seven symptoms were rated “0” or “1” for at least 21.5 hours.⁴ Safety was assessed by the percentage of adverse events that occurred. They were rated using a graded scale of 1-3 according to the Division of AIDS table for grading adult and pediatric adverse events. Grades 1-3 represented mild, moderate, and severe ratings of the events, respectively and intergroup comparison was made using the Fischer’s exact test.^{4,5}

5. Results

Each study compared 300mg Peramivir differently than the other. The open label study compared 300mg Peramivir, twice daily, to 600mg Peramivir, once daily alone, the Kohno et al⁴ RCT, compared both Peramivir groups, single dose, to placebo, and the Kohno et al⁵ RCT, compared both Peramivir groups to 75mg Oseltamivir. All studies were conducted in hospital settings involving subjects with confirmed influenza virus. Ison et al¹, included the widest range

of patients ages (14-92) compared to Kohno et al⁴ (20-64) and Kohno et al⁵ (20-80). Efficacy endpoint results in all studies were represented by continuous data and provided p-values and confidence intervals. Safety endpoints for all of the studies were able to be converted to dichotomous data thus relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH) were calculated for this review for safety.

In Ison et al¹, 234 subjects were randomized into two groups, 300mg Peramivir and 600mg Peramivir. Four withdrew before treatment and from the remaining population 127 subjects had confirmed influenza thus leaving the intent to treat population to be 127 subjects. The study utilized the Kaplan-Meier method in order to measure time to alleviation of symptoms amongst the subjects. In the 300mg Peramivir group the median time in hours was 135 (95% CI:89,184) compared to the 600mg Peramivir group of 158 (95% CI:103,306). Safety was measured by documenting the number of adverse events experienced in the groups. The 300mg Peramivir group displayed 90 adverse events total (79% of the group) and the 600mg Peramivir group showed 85 adverse events total (73%). The relative risk increase calculated was 8% and the absolute risk increase was 6% (Table 2). The numbers needed to harm was calculated to be 17. This means for every 17 patients who took Peramivir 300mg, there was one more incidence of an adverse event than those who took Peramivir 600mg. There were a total of 22 deaths recorded in the study, 8 deaths in the 300mg group and 14 deaths in the 600mg group.¹

In Kohno et al⁴, 300 total subjects were randomly allocated to two groups receiving Peramivir (300mg or 600mg) and one group receiving placebo. Of the total 300 subjects, 4 subjects had withdrawn from the study thus resulting in 296 subjects in the intent to treat population. Two subjects withdrew after allocation to groups but before treatment, one subject did not have any symptom assessment data, and one subject lacked laboratory confirmed

influenza virus. The study utilized Cox proportional-hazards modeling to calculate a hazard ratio which compares the study groups to placebo. The hazard ratio for time to alleviation of symptoms for the 99 subjects in the 300mg Peramivir group and the 97 subjects in the 600mg Peramivir group was 0.681 (95% CI:0.511-0.909, $p=0.0092$) and 0.666 (95% CI:0.499-0.890, $p=0.0092$), respectively. This is a significant difference showing both groups of Peramivir had more of an effect on decreasing the time to alleviation of symptoms in comparison to the placebo group. The efficacy is further assessed and compared when viewing the median time, in hours, for alleviation of symptoms in each group. The 300mg Peramivir group displayed alleviation within a median of 59.1 (95% CI:50.9-72.4) compared to 600mg Peramivir and placebo which resulted in 59.9 (95% CI:54.4-68.1) and 81.8 (95% CI: 68.0-101.5), respectively. P- values were adjusted and applied to make intergroup comparisons between the Peramivir groups. There was no significant difference for efficacy between both dosages of Peramivir which is displayed by an adjusted p- value of 0.0092.⁴

For assessment of safety the Kohno et al⁴ study used the Fischer's exact test to calculate the p- value for comparing Peramivir with placebo groups. All drugs were generally well tolerated by all groups and no evidence displayed a significant difference between them. The incidence of adverse events compared to placebo was calculated to be $P=0.4986$ for the 300mg Peramivir group and $P=1.000$ for the 600mg Peramivir group. In terms of number of adverse events occurring during the study, the Peramivir groups recorded 252 events each while placebo recorded 257. The most commonly observed adverse events throughout all groups were gastrointestinal. Diarrhea occurred in 14.1% in the 300mg group, 15.2% in the 600mg group, and 17.0% in the placebo group. There were a total of 10 severe adverse events recorded in all groups, with QT prolongation being the most common occurrence (two subjects in the 300mg

group, one subject in 600mg group, and three subjects in the placebo). The 600mg group further included one subject developing increased blood glucose and one subject with increased blood creatinine. Placebo displayed one subject with increased blood pressure and one subject with increased blood glucose.⁴ The relative risk increase, absolute risk increase and numbers needed to harm were calculated to be -3.3%, -3%, and -34, respectively (Table 2).

In the Kohno⁵ study, 1,099 patients were assigned randomly to the three treatment groups of 300mg Peramivir, 600mg Peramivir, and 75mg Oseltamivir. Two patients lacked post treatment efficacy data and eight patients dropped out before treatment, leaving 1,091 patients in the intent to treat population (364 receiving 300mg, 362 receiving 600mg, and 365 receiving Oseltamivir). The primary efficacy endpoint was calculated using the Cox proportional-hazards model to compare Peramivir groups to Oseltamivir. Noninferiority of the Peramivir groups to Oseltamivir was exhibited by hazard ratios of 0.946 (97.5% CI:0.793-1.129) for 300mg Peramivir group and 0.970 (97.5% CI:0.814-1.157) for the 600mg Peramivir group. Time to alleviation of symptoms, in hours, for the 300mg Peramivir, 600mg Peramivir, and 75mg Oseltamivir groups were 78.0 (95% CI:68.4-88.6), 81.0 (95% CI:72.7-91.5), and 81.8 (95% CI:73.2-91.1), respectively.⁵

In terms of safety, Kohno et al⁵ demonstrated incidence of adverse events for the 300mg Peramivir, 600mg Peramivir, and Oseltamivir groups as 14.0%, 18.1%, and 20.0%, respectively. This showed the 300mg Peramivir group to be significantly safer in terms of adverse events than the Oseltamivir group whereas the 600mg Peramivir group was insignificantly less. Adverse effects of serious stature were most commonly QT prolongation with no significant difference between the three groups. QT prolongation occurred in 5 subjects receiving 300mg Peramivir, 8 subjects receiving 600mg Peramivir, and 10 subjects receiving Oseltamivir.⁵ As mentioned in

table 2, the relative risk increase, absolute risk increase, and numbers needed to harm were -22%, -15%, -7%, respectively. This negative value for NNH means for every 7 patients who took Peramivir 300mg, there was one fewer incidence than those who took Peramivir 600mg.

Table 2 - Harm effects

Study	CER	EER	RRI	ARI	NNH
Ison et al ¹	73%	79%	8%	6%	17
Kohno et al ⁴	90.9%	87.9%	-3.3%	-3%	-34
Kohno et al ⁵	66%	51%	-22%	-15%	-7

6. Discussion

The efficacy and safety of 300mg Peramivir was the scope of this review when analyzing all three studies. Currently, a single dose of 600mg Peramivir is used for treatment in acute uncomplicated influenza in adult patients.⁶ The 600mg Peramivir is directed to be intravenously infused for 15-30 minutes.⁶ Thus comparison between the dosages of Peramivir was an important aspect to address for consideration of 300mg Peramivir.

In Ison et al¹, 300mg twice daily, Peramivir displayed less median time to alleviation of symptoms compared to the 600mg once daily, Peramivir. It can be argued that there is not enough statistical evidence in this study to determine a superiority between the two groups since the study did not provide p-values. As far as safety, it seems there is no significance between both Peramivir groups. Being this was an open label study, there stood no placebo or baseline to compare the data collected.

In Kohno et al⁴, both Peramivir groups exhibited statistical evidence of superiority in efficacy compared to placebo. The Peramivir groups once again did not show a significant difference between each other. As far as safety, all three groups in the study displayed similar adverse events.

Kohno et al⁵ study had also displayed superiority of the efficacy endpoint in both Peramivir groups in comparison to Oseltamivir. There was not as much statistical significance in this study to prove this point compared to the last study mentioned above. The safety endpoint showed the most differentiation compared to the other studies. The 300mg Peramivir group had a more significant percentage of subjects without adverse events than the Oseltamivir group.

Limitations were found in the three studies concerning population, exclusion criteria and comparison groups. All three studies differed in the populations of subjects with Ison et al¹ including the United States, Canada, Mexico, Australia, and New Zealand, Kohno et al⁴ including only Japan, and Kohno et al⁵ focusing on subjects from Japan, South Korea and Taiwan. Though Japan was included in two of the three studies this may not provide efficient overlap of patient population. Population is important in this review also because of the existence of different influenza strains in each region of the world. Keeping this a constant could show change in the outcomes and possibly leading to more concise results for specific populations.

In terms of exclusion criteria, potential limitation could have existed when considering protocol taken. In Ison et al¹ the enrollment criteria was more broad thus leading to the possibility of more severely ill patients involved. In Kohno et al⁴, the enrollment criteria was more specific and led to exclusion of high risk patient populations. This could have resulted in different outcomes for time to alleviation of symptoms due to severely ill patients potentially taking longer to resolve symptoms. Also, the criteria of Ison et al¹ incorporated a population with a broader variation in strain. A major portion of the subjects suffered from the 2009 H1N1 pandemic strain along with subjects infected with seasonal influenza strains.

7. Conclusion

After analyzing and reviewing the results provided in the three studies, intravenous

300mg Peramivir is effective and safe for treatment in seasonal influenza. Though, 300mg Peramivir did not show significant evidence of superior efficacy compared to 600mg groups, the argument can be made that showing noninferiority is sufficient to allocate further research for the use of 300mg Peramivir and show effectiveness. Not all studies provided enough statistical evidence to state 300mg Peramivir as the clear leader amongst all comparison groups. To further the argument of 300mg Peramivir to be considered as a treatment option, Ison et al¹ demonstrated that giving Peramivir at doses of 300mg compared to a single dose of 600mg Peramivir for multiple days did result in less time to alleviation of symptoms. By displaying noninferiority to 600mg Peramivir and 75mg Oseltamivir, 300mg Peramivir demonstrated an ability to be as effective as the treatment options approved at this time. All of the studies showed the safety endpoint in all groups were not significant. One group did not seem to exhibit an excess of adverse events over the others.

For future research I would recommend studies to be conducted using populations and exclusion criteria that are close in detail. I recommend conducting randomized controlled trials that only include either high risk or previously healthy patients from the United States with similar influenza strains. In this manner, 300mg Peramivir may be more accurately assessed for usage.

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